REMARKS

The claims are not amended with this paper. Currently pending in the application are claims 1, 7-9, 14, 15, 19-22 and 27-29.

The Office Action

Applicants note that the Office Action appears to largely repeat the rejections of prior Office Actions, in particular the Office Action of July 27, 2007. Applicants respectfully submit that, in the Response to that Office Action (filed August 25, 2008, together with a Request for Continued Examination), Applicants reiterated certain arguments but also provided additional discussion responsive to the rejections of record; however, the Office Action does not appear to address or even acknowledge those new arguments.

As provided in MPEP 707.07(f), "Where the applicant traverses any rejection, the examiner should, if he or she repeats the rejection, take note of the applicant's argument and answer the substance of it" (emphasis added). Applicants respectfully contend that the Office Action dated November 13, 2008, does not comply with MPEP 707.07(f), at least because the Office Action fails to take note of the new arguments and answer the substance of them. Applicants respectfully request that any further Office Action take note of all arguments and answer the substance of them.

Rejections Under 35 U.S.C. § 103

(i) Claims 1, 9, 14, 15, 19-22, and 27 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over United States Patent No. 5,589,480 to Elkhoury, *et al.* ("Elkhoury"), in view of United States Patent No. 5,849,761 to Yaksh ("Yaksh"), United States Patent No. 5,840,731 to Mayer, *et al.* ("Mayer"), United States Patent No. 5,635,204 to Gevirtz, *et al.* ("Gevirtz") and T. Lin, *et al. Can. J. Anesth.* Feb. 1998, 45(2), pages 175-177 ("Lin"). Applicants respectfully disagree and traverse.

To properly determine a *prima facie* case of obviousness, the Examiner "must step backward in time and into the shoes worn by the hypothetical 'person of ordinary skill in the art' when the invention was unknown and just before it was made." M.P.E.P § 2142. This is important, as "impermissible hindsight must be avoided and the legal

conclusion must be gleaned from the prior art." *Id.* Although Applicants do not agree that the references cited in the Office Action teach every element of the claims, "Knowledge in the prior art of every element of a patent claim ... is not of itself sufficient to render the claim obvious." *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966); *Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1333-34 (Fed. Cir. 2002).

The claimed invention provides topical pharmaceutical compositions and methods of providing analgesia comprising morphine and a tolerance-attenuating dosage of ketamine sufficient to yield a dose-lowering effect on morphine.

The Office Action alleges that Elkhoury teaches a topical composition of morphine that provides an analgesic effect in a localized area without migration to the bloodstream. Elkhoury does not teach a topical pharmaceutical composition comprising a combination of morphine and ketamine, let alone a tolerance-attenuating dosage of ketamine sufficient to yield a dose-lowering effect on morphine. Elkhoury also does not teach or suggest the use of topical compositions for effectively delivering ketamine and morphine to local peripheral receptors and not to central receptors, as required by the pending claims.

The Office Action relies on Yaksh, Mayer, Gevirtz and Lin to rectify the deficiencies of Elkhoury. In particular, the Office Action alleges that: Yaksh teaches the use of low dosages of morphine to avoid CNS side effects; Mayer teaches the addition of ketamine to enhance analgesia and/or reduce side effects; Gevirtz teaches the use of ketamine for topical administration; and Lin teaches the combination of ketamine, morphine and bupivacaine. Applicants disagree with the position taken by the Office Action. Applicants contend that none of the cited references, alone or in combination, can "bridge the gap" between the teachings of Elkhoury and the subject matter of the pending claims. In particular, none of the references teaches or suggests the use of topical compositions and methods for effectively delivering ketamine and morphine to local peripheral receptors and not to central receptors, as required by the pending claims.

With regard to Yaksh, the Office Action concedes that Yaksh teaches the disadvantage of the use of morphine in that it is taught to have short duration of activity and to have systemic and CNS side effects when used at high levels. Applicants

respectfully submit that Yaksh teaches away from the use of morphine at all. Indeed, Yaksh states that "other opioids, such as morphine, that readily cross the blood brain barrier could be effective as anti-hyperalgesics, but their permeability through the blood brain barrier results in abuse liability" (Column 4, lines 45-49) and that "the compositions provided herein, contain opioids that do not, upon topical or local administration, substantially cross the blood brain barrier..." (Column 4, lines 50-53). Applicants contend that Yaksh suggests to one of ordinary skill in the art that the use of morphine (as required by the pending claims) is contraindicated due to the possibility that morphine could cross the blood brain barrier, resulting in abuse liability. Indeed, Yaksh states that "conventional opioids [are] unsuitable for local administration" (paragraph bridging Columns 3-4). Applicants contend that this is a clear teaching away from the presently-claimed methods. Furthermore, Yaksh does not teach or suggest the use of topical compositions or methods for effectively delivering ketamine and morphine to local peripheral receptors and not to central receptors, as required by the pending claims. In view of these teachings (or lack thereof), one of ordinary skill in the art would have lacked the motivation to combine Yaksh with Elkhoury (or the other cited references) to arrive at the subject matter of the pending claims.

With regard to Mayer, the Office Action alleges that Mayer teaches that the analgesic effectiveness of a combination drug composition comprising at least one analgesic (for example, morphine) is significantly enhanced by the addition of an NMDA receptor antagonist (for example, ketamine). It is important to note that Mayer is limited to the discussion of compositions comprising both an analgesic (either opioid or non-opioid) and a second component chosen from a sedative, a muscle relaxant or a non-opioid analgesic. Moreover, Mayer does not disclose the use of topical compositions or methods for effectively delivering ketamine and morphine to local peripheral receptors and not to central receptors, as required by the pending claims. Mayer discloses systemic means of administration, not topical administration. Accordingly, one of ordinary skill in the art would not appreciate, based on a reading of Mayer (taken alone or together with the other cited references), that morphine could be administered concurrently with a tolerance-attenuating dose of a ketamine, to local peripheral receptors, to attenuate, reverse, or prevent tolerance to analgesics.

With regard to Gevirtz, although the Office Action alleges that Gevirtz teaches the use of ketamine for topical administration, Applicants contend that Gevirtz is directed to a method of inducing surgical anesthesia via transdermal administration of an amnesia-producing drug and, subsequently, an anesthesia-producing drug. Applicants submit that the transdermal administration according to Gevirtz results in a central (systemic) effect, not a local (peripheral) effect. Gevirtz teaches that ketamine is useful to produce "amnesia", a central effect. In any case, Gevirtz does not disclose a tolerance-attenuating dose of ketamine when administered in combination with morphine. In fact, Gevirtz neither teaches nor suggests tolerance attenuation or the need therefor. Accordingly, Gevirtz could not teach or suggest to one of ordinary skill in the art that morphine could be administered concurrently with a tolerance-attenuating dose of a ketamine in a topical formulation to attenuate, reverse, or prevent tolerance to analgesics. One of ordinary skill in the art would not understand Gevirtz (taken alone or together with the other cited references) to teach or suggest the use of topical compositions or methods for effectively delivering ketamine and morphine to local peripheral receptors and not to central receptors, as required by the pending claims.

With regard to Lin, the Office Action alleges that Lin teaches that it is well known in the art that an NMDA receptor antagonist can abolish nociceptor hypersensitivity. As Applicants understand the reference, Lin describes the use of spinal (i.e., central) delivery of certain compositions. Lin (whether taken alone or together with the other cited references) does not teach or suggest the use of topical compositions or methods for effectively delivering ketamine and morphine to local peripheral receptors and not to central receptors, as required by the pending claims.

None of Elkhoury, Yaksh, Mayer, Gevirtz and Lin alone, or in any combination, teaches or suggests topical pharmaceutical compositions for effectively delivering ketamine and morphine to local peripheral receptors and not to central receptors, as required by the pending claims, nor methods of providing analgesia comprising morphine and a tolerance-attenuating dosage of ketamine sufficient to yield a dose-lowering effect on morphine, wherein the morphine and ketamine function through local peripheral receptors and not central receptors, as required by the pending claims.

Applicants submit that none of the references cited in the Office Action teaches or suggests that the interaction between NMDA receptors and opiates occurs peripherally. Thus, there would be no expectation that a tolerance-attenuating amount of ketamine could be delivered to local peripheral receptors and have a dose-lowering effect on the morphine, as recited by the present claims. It would therefore not have been obvious for the skilled artisan to combine the teachings of the cited references as stated in the Office Action, nor would one of ordinary skill in the art be motivated to modify the teachings of Elkhoury in light of Yaksh, Mayer, Gevirtz and Lin to arrive at the claimed invention. Furthermore, one of ordinary skill would not have had a reasonable expectation that topical pharmaceutical compositions for effectively delivering ketamine and morphine to local peripheral receptors and not to central receptors would have a dose-lowering effect on the morphine.

For at least the foregoing reasons, reconsideration and withdrawal of the rejection is proper and such action is respectfully requested.

(ii) Claims 7, 8, 28, and 29 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Elkhoury, Yaksh, Mayer, Gevirtz and Lin, in further view of United States Patent No. 5,322,683 to Mackles et al. ("Mackles").

As discussed above, none of Elkhoury, Yaksh, Mayer, Gevirtz and Lin alone, or in combination, teach or suggest topical pharmaceutical compositions and methods of providing analgesia by effectively delivering ketamine and morphine to local peripheral receptors and not to central receptors, to yield a dose-lowering effect on morphine, as required by the pending claims.

In regard to Mackles, the Office Action alleges that Mackles teaches that lidocaine is a topical analgesic. Mackles does not teach or suggest the use of lidocaine in combination with any other active ingredients, let alone morphine and a tolerance-attenuating dosage of ketamine sufficient to yield a dose-lowering effect on morphine. Mackles does not teach or suggest the use of topical compositions for effectively delivering ketamine and morphine to local peripheral receptors and not to central receptors, as required by the pending claims. In short, Mackles does not remedy the deficiencies of the other references discussed above, and cannot render obvious claims

7, 8, 28, and 29. Accordingly, reconsideration and withdrawal of the rejection to claims 7, 8, 28, and 29 under 35 U.S.C. § 103 is respectfully requested.

Double Patenting Rejections

Claims 1, 7-9, 14, 15, 19-22 and 27-29 stand rejected on the grounds of nonstatutory obviousness-type double patenting over claims 2 and 11-15 of United States Patent No. 6,825,203. Claims 1, 9, 14, 15, 19-22 and 27 further stand provisionally rejected on the grounds of nonstatutory obviousness-type double patenting over claims 27-35 of copending U.S. Application Serial No. 10/823,365.

While Applicants contend that the present claims are allowable for at least the reasons discussed above, it still remains unknown whether the subject matter presently claimed will be deemed allowable in the present application. Therefore, Applicants respectfully traverse these rejections, and (without agreeing with the rejections) maintain the request that these rejections be held in abeyance until the application is otherwise in condition for allowance.

CONCLUSION

For at least the foregoing reasons, Applicants believe the pending application is in condition for allowance. Early and favorable action is earnestly requested.

Applicants conditionally petition for any extension of time necessary for consideration of this response. The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 04-1105, under Order No. 62072 (51590).

Respectfully submitted,

Date: May 13, 2009

By: /Mark D. Russett/

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